PART FIVE

CIGARETTE SMOKING, NICOTINE AND CARBON MONOXIDE

IX. Acute Circulatory Effects of Cigarette Smoking.

X. Acute and Chronic Effects of Nicotine.

XI. Circulatory Effects of Carbon Monoxide.

In the preceding sections, the differences between smokers and nonsmokers have been discussed. The observations relating to the acute effects of smoking are considered in the present sections. These include not only the effects of cigarette smoke but also those of its constituents, namely, nicotine and carbon monoxide. The other chemicals present in cigarette smoke have been omitted, since hardly any report has been made of their action on the circulatory system.

The experimental observations discussed in these sections also include the chronic administration of smoke, nicotine and carbon monoxide to animals. The problem in these experiments is how to relate the results to smokers who develop coronary heart disease. Unfortunately, the amounts of nicotine and carbon monoxide administered to animals far exceed those which are absorbed during ordinary forms of smoking.

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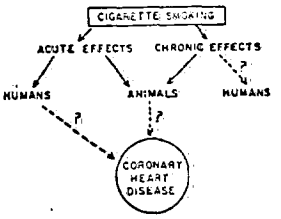
IX. ACUTE CIRCULATORY EFFECTS OF SMOKING



IX CIGARETTE SMOKING

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To prove that smoking causes coronary heart disease, it is necessary to be able to reproduce the disease in the laboratory. So far, this has not been possible in animals. The animals subjected to chronic exposure to cigarette smoke have been few in number and the observations have been limited entirely to postmortem examination. Acute exposure has been performed largely on animals and humans without heart disease, so that it is difficult to relate the results to the disease state. Chronic exposure of humans to smoking is an impossible experiment because other risk factors are operative in habitual smokers.

The investigations of acute effects of smoking has been more significant in excluding rather than proving that it causes coronary heart disease. Smoking does not cause reduction of coronary blood flow, which is the primary hemodynamic defect in coronary heart disease. Smoking acutely increases blood pressure, whereas the habitual smoker is not hypertensive.

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Although patients with coronary heart disease show persistent elevation of the blood lipid level, habitual smokers do not necessarily experience this and smoking acutely does not consistently produce an elevation. Acute smoking increases blood coagulability in normal subjects and has not been thoroughly investigated in patients with coronary heart disease. The basis for these generalizations appears in the following sections. The Additional Bibliographic List relates to the reasons and manner of stopping the habitual use of cigarettes:

List No. 24. Cessation of cigarette smoking.

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IX. CARDIOVASCULAR EFFECTS OF SMOKING

Additional Bibliographic List No. 24

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IX-A. Cardiac Function

The influence of cigarette smoking on heart rate, cardiac output, stroke volume, myocardial contractility and metabolism is the primary concern of this section. However, each parameter will not be discussed separately but according to the manner in which it is derived. The technique of measuring cardiac output and the status of the subject, whether healthy or with coronary heart disease, are considered in the grouping. In investigations on animals, the acute are separated from the chronic.

1. Electrocardiogram. The most consistent effect of smoking in normal subjects is tachycardia (Grabiel et al., 1938; Buxtorf and Beaumont, 1968). The electrocardiogram of some patients with coronary heart disease shows inversion of the T wave and alteration of the QRS complex (Tobiasch, 1951; Kaltenback et al., 1967; Serafimova, 1971). The apexcardiogram (Aronow, 1971) and chronodynogram (Raab et al., 1960) have been applied and the results are similar to those of the electrocardiogram.

2. Ballistocardiogram. The early investigations on the effects of cigarette smoking involved the use of the ballistocardiogram (BCG) for the estimation of cardiac output (see Starr (1960, 1967) and Jackson et al., (1967)). The first application was reported by Henderson (1953), using subjects from the Hospital of the University of Pennsylvania. After smoking a single cigarette, the subject showed an increase in pulse rate but the form of the BCG remained normal in each of 50 healthy young adults. In 30 older persons believed to be healthy, there was a temporary abnormality of the

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ballistocardiogram in 4 instances. In 40 patients with coronary heart disease, the BCG became abnormal or more abnormal in form after smoking in 38% of these cases. No description was given of the smoking habits of subjects.

A group of 113 medical students, of whom 82 were smokers, were investigated by Thomas et al. (1956). A statistically significant change was noted in systolic, diastolic and pulse pressures, heart rate, stroke volume and cardiac output. There was no difference between smokers and nonsmokers. Among subgroups there were striking differences which were associated with family history. Subjects with parental hypertension, whose control cardiac output was large prior to smoking, showed more than twice as great an increase as did subjects with negative parents. Subjects with a parental history of coronary heart disease had very little increase in cardiac output in contrast to subjects with negative parents. In additional reports the investigators were able to reproduce their results (Thomas and Murphy, 1958, 1960a, 1960b).

The following investigations have confirmed most of the conclusions reported above: Levy et al. (1947) in 27 normal subjects and 21 patients with coronary heart disease; Russek et al. (1955) in 28 normal subjects and 37 patients; Davis et al. (1956) in 25 normal subjects and 190 patients with coronary heart disease; Dec (1960) in 15 normal subjects and 20 patients with myocardial infarction; Simon and Iglauer (1960, 1961) in 14 males without heart disease; Hanson (1962) in 3 patients with angina; Klensch (1963)

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in 39 subjects; Markewicz (1966) in 45 students; Buchanan (1969) in 19 young adults with coronary heart disease.

3. Dye Dilution Technique. The first application of a modern method for measuring cardiac output was accomplished by Irving and Yamamoto (1963). The smoking of one cigarette caused an increase in cardiac output in 15 normal subjects (Edmundowicz et al., 1964; Frankl et al., 1965). Pentecost and Shilingford (1964a, 1964b) compared subjects with patients. The healthy men and those with angina in the absence of infarction behaved similarly with an increase in cardiac output. However, some patients among the postinfarction group showed a marked fall in stroke volume and cardiac output while smoking.

Two procedures reduce the response of normal subjects to smoking. The previous administration of propranolol, a beta adrenergic blocker, decreased the intensity of cardiac output response (Frankl and Soloff, 1967). Pretreatment with glucose diminished the cardiac output response (Moses et al., 1964; Soloff and Powers, 1964). The explanation for the latter is not apparent but the influence of propranolol is related to its blockade of the cardiac effects of nicotine.

4. Coronary blood flow and myocardial metabolism. It has been supposed that cigarette smoking causes coronary spasm. This was disproven by catherization of the coronary sinus in man by Bargeron et al. (1957). Cigarette smoking in 30 normal subjects caused a significant rise in coronary blood flow, a decline in coronary vascular resistance and

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myocardial extraction of glucose and oxygen. In 7 males with myocardial infarction, smoking still caused an increase in blood pressure and heart rate. In 3 of the patients, coronary blood flow did not change, while in 3 others it fell slightly (Regan et al., 1960a, 1960b, 1961). Although there was slight increase in oxygen consumption in 3 cases, the myocardial efficiency was also increased. The data reported illustrate that in patients with coronary heart disease smoking results in no reduction of myocardial efficiency. In 15 patients with angiographically demonstrated severe obstructive coronary artery disease, cigarette smoking did not induce lactate production by the heart (Summers et al., 1971). There was no evidence of ischemia as determined by abnormalities in lactate extraction.

5. Exercise and the heart. Exercise has been used as a form of stress to detect borderline patients with coronary heart disease (Davis et al., 1953; Davis, 1959; Gusman and Khalfen, 1959). In subjects without clinical evidence of coronary heart disease, smoking does not interfere with their capacity to perform moderate exercise (see Section VII-A). There are observations which indicate that certain forms of exercise by particular individuals elicit responses which differ from the normal.

a. Exercise by bicycle ergometer severe enough to produce a fivefold increase in oxygen uptake of young male smokers caused an oxygen debt accumulation greater than that of nonsmokers. The oxygen debt of nonsmokers was 6.5% of the total increase in oxygen uptake, while for smokers it was 24.7% (Chevalier et al., 1963). In another group of subjects

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the same investigators (Krumholz et al., 1964) again reported an increase in oxygen debt but also a decrease in lung function, which were not noted previously. They also reported a decrease in diffusing capacity of the lung both at rest and with exercise. The exercise was more severe and reached up to 2 l/min, whereas in the first series it was 1.4 l/min. Since oxygen uptake is five- to sevenfold from a resting value of 0.3 l/min, this would be equivalent to running a race which is not ordinarily accomplished in the normal course of activity. It is necessary to measure oxygen uptake at various levels of exercise to determine the threshold for the increase in oxygen debt. The relation of activity to oxygen usage has been reviewed by Naughton (1967).

b. Smoking by patients with a healed myocardial infarction did not alter cardiac output significantly/ whether at rest or during exercise (Frankl et al., 1965a, 1965b). The lack of response in this group can be interpreted either way. The absence of an increase would mean that the infarcted heart has become tolerant to smoking. It can also mean that the heart has lost its capacity to respond, which is not valid since the subjects still showed an increase in output during exercise.

6. Canine heart. The dog has been the species most widely used in these investigations. In 1941, Bellet et al. studied dogs with chronic ligation of one coronary artery to simulate infarction occurring in man. Inhalation of cigarette smoke at 1/4 the dose administered prior to the infarction caused electrocardiographic changes. Thirty years later

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Bellet et al. (1972a) repeated the same experiments but measured the electrical threshold for ventricular fibrillation. After 30 minutes of exposure to smoke, the threshold to infarction was reduced. A similar effect was observed after administration of caffeine (Bellet et al., 1972b).

In an open-chest dog, the administration of cigarette smoke caused a brief decrease in oxygen utilization by the heart, but an increase in coronary blood flow (Kien et al., 1958; Kien and Sherrod, 1960). This coincided with the onset of irregularities which appeared early during the inhalation. This is different from the phenomenon reported by Bellet et al., which required 30 minutes for the reduction in the threshold to fibrillation to appear. The experiments reported by others on cigarette smoking in dogs confirm essentially the results in man, such as, tachycardia (Kaymakcalan et al., 1968), increase in coronary blood flow (Haft et al., 1966), and blockade of cardiac effects by propranolol (Edmundowicz et al., 1965; Westfall et al., 1966).

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Auerbach et al. (1967, 1971) and Hammond et al. (1970) have reported thickening of myocardial aterioles in beagles that have been exposed to cigarette smoke for several months. It is unfortunate that no measurements of cardiac function were made in animals prior to their being sacrificed. Reece and Ball (1972) subjected 7 dogs to exposure to cigarette smoke and treadmill exercise daily for one year. The electrocardiograms indicated enlargement of the heart. There was also thickening of the myocardial arterioles in 5 of the 7 dogs. However, no hemodynamic measurements were made

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similar to those completed in man.

7. Other animal species. Haag et al. (1960) exposed rats to cigarette smoke for their entire life span and they showed no significant differences in blood pressure, longevity and reproduction as compared with unexposed rats. No lesions were noted at autopsy. Myocardial lesions have been reported after chronic exposure to cigarette smoke in guinea pigs (Lupu and Velican, 1961, 1962) and mice (Komczynski, 1958). Ratcliffe (1965) examined coronary arteries of animals that died in the Philadelphia Zoological Garden during the period 1944 to 1964. The frequency of coronary arterial disease reflects the effects of physiological and psychological responses to social stimuli and environmental pollution. These animals were not exposed to cigarette smoke.

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IX-B. Blood Pressure and Peripheral Blood Flow

The early observations on the effect of tobacco smoke on blood pressure in man and animals have been summarized by Lee (1908). The response has been subsequently verified and standardized as the "smoking test" in humans (Thomas and Murphy, 1959; Kaufman et al., 1959; Roth and Shich, 1960). After the smoking of 1 cigarette, the rise in blood pressure, acceleration of heart rate and reduction of skin temperature are regarded as furnishing an assessment of the status of the lability of the circulatory system. An exaggerated response is interpreted as a sign of essential hypertension. This test, like the cold pressor test, is no longer widely used.

Among healthy subjects, the rise in blood pressure in response to cigarette smoking is greater and lasts longer in smokers than in nonsmokers (Keriigan et al., 1968). The hemodynamic cause of the rise in blood pressure is predominantly an increase in cardiac output rather than an increase in peripheral vascular resistance (Marshall et al., 1966, 1969; Goldberg et al., 1971; Krone et al., 1972; Wysonkinski, 1971). This conclusion is based on observations in normal subjects. Patients with angina pectoris after smoking and exertion also show a rise in blood pressure (Aronow and Swanson, 1969).

Although there is no increase in total vascular resistance following smoking, the blood vessels of the extremities show vasoconstriction. The following techniques have been applied: capillary circulation of the nail fold (Wright, 1933), hand plethysmograph (Lampson, 1935; Mulinos and

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Shulman, 1940; Shepherd, 1951), calf plethysmograph (Matsubara and Sano, 1972); cutaneous temperature (Moyer and Maddock, 1940; Roth and Shick, 1960; Furey et al., 1967), clearance of radioactive tracers in the extremity (Friedell, 1953; Coffman and Javett, 1963), direct microscopy of mucosa (Asano and Branemark, 1970) and electrical impedance (Allison and Roth, 1969). In patients with peripheral vascular disease the plethysmograph technique (Barnett and Boake, 1960) and the skin-temperature technique have been used extensively (Fleig, 1908; Hines, 1960; Wood, 1960, Freund and Ward, 1960; Zannini et al., 1963; Stallworth et al., 1967).

The vasoconstriction associated with cigarette smoking can be reduced in subjects who have been pretreated with reserpine (Westfall and Watts, 1961, 1962). The explanation is that depletion of catecholamnes by reserpine interferes with the primary action of nicotine (see Section X). The effect of smoking is vasodilatation in the cerebral (Kuhn, 1967; Miyazaki, 1969) and ophthalmic (Bettman et al., 1958) blood vessels. The reason for the lack of vasoconstriction in these areas is not known.

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B. Blood Pressure and Peripheral Blood Flow

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